

LEUPROLIDE ACETATE - leuprolide acetate injection

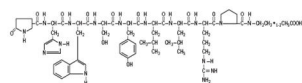
Teva Parenteral Medicines, Inc

Package Insert

Rx Only

DESCRIPTION

Leuprolide acetate is a synthetic nonapeptide analog of naturally occurring gonadotropin releasing hormone (GnRH or LH-RH). The analog possesses greater potency than the natural hormone. The chemical name is 5-oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-leucyl-L-leucyl-L-arginyl-N-ethyl-L-prolinamide acetate (salt) with the following structural formula:



Leuprolide acetate injection is a sterile, aqueous solution intended for subcutaneous injection. It is available in a 2.8 mL multiple-dose vial containing 5 mg/mL of leuprolide acetate, 6.3 mg/mL sodium chloride, USP for tonicity adjustment, 9 mg/mL of benzyl alcohol as a preservative and water for injection, USP. The pH may have been adjusted with sodium hydroxide, NF and/or acetic acid, NF.

CLINICAL PHARMACOLOGY

Leuprolide acetate, an LH-RH agonist, acts as a potent inhibitor of gonadotropin secretion when given continuously and in therapeutic doses. Animal and human studies indicate that following an initial stimulation of gonadotropins, chronic administration of leuprolide acetate results in suppression of ovarian and testicular steroidogenesis. This effect is reversible upon discontinuation of drug therapy. Administration of leuprolide acetate has resulted in inhibition of the growth of certain hormone dependent tumors (prostatic tumors in Noble and Dunning male rats and DMBA-induced mammary tumors in female rats) as well as atrophy of the reproductive organs. In humans, subcutaneous administration of single daily doses of leuprolide acetate results in an initial increase in circulating levels of luteinizing hormone (LH) and follicle stimulating hormone (FSH), leading to a transient increase in levels of the gonadal steroids (testosterone and dihydrotestosterone in males, and estrone and estradiol in pre-menopausal females). However, continuous daily administration of leuprolide acetate results in decreased levels of LH and FSH. In males, testosterone is reduced to castrate levels. In pre-menopausal females, estrogens are reduced to post-menopausal levels. These decreases occur within two to four weeks after initiation of treatment, and castrate levels of testosterone in prostatic cancer patients have been demonstrated for periods of up to five years.

Leuprolide acetate is not active when given orally.

Pharmacokinetics

Absorption

Bioavailability by subcutaneous administration is comparable to that by intravenous administration.

Distribution

The mean steady-state volume of distribution of leuprolide following intravenous bolus administration to healthy male volunteers was 27 L. In vitro binding to human plasma proteins ranged from 43% to 49%.

Metabolism

In healthy male volunteers, a 1 mg bolus of leuprolide administered intravenously revealed that the mean systemic clearance was 7.6 L/h, with a terminal elimination half-life of approximately 3 hours based on a two compartment model.

In rats and dogs, administration of ¹⁴C-labeled leuprolide was shown to be metabolized to smaller inactive peptides, a pentapeptide (Metabolite I), tripeptides (Metabolites II and III) and a dipeptide (Metabolite IV). These fragments may be further catabolized.

The major metabolite (M-I) plasma concentrations measured in 5 prostate cancer patients reached maximum concentration 2 to 6 hours after dosing and were approximately 6% of the peak parent drug concentration. One week after dosing, mean plasma M-I concentrations were approximately 20% of mean leuprolide concentrations.

Excretion

Following administration of leuprolide acetate for depot suspension 3.75 mg to 3 patients, less than 5% of the dose was recovered as parent and M-I metabolite in the urine.

Special Populations

The pharmacokinetics of the drug in hepatically and renally impaired patients has not been determined.

Drug Interactions

No pharmacokinetic-based drug-drug interaction studies have been conducted with leuprolide acetate. However, because leuprolide acetate is a peptide that is primarily degraded by peptidase and not by cytochrome P-450 enzymes as noted in specific studies, and the drug is only about 46% bound to plasma proteins, drug interactions would not be expected to occur.

Clinical Studies

In a controlled study comparing leuprolide acetate injection 1 mg/day given subcutaneously to DES (diethylstilbestrol), 3 mg/day, the survival rate for the two groups was comparable after two years of treatment. The objective response to treatment was also similar for the two groups.

INDICATIONS AND USAGE

Leuprolide acetate injection is indicated in the palliative treatment of advanced prostatic cancer.

CONTRAINDICATIONS

Leuprolide acetate injection is contraindicated in patients known to be hypersensitive to GnRH, GnRH agonist analogs or any of the excipients in leuprolide acetate injection. Reports of anaphylactic reactions to GnRH agonist analogs have been reported in the medical literature.^{1, 2}

Leuprolide acetate injection is contraindicated in women who are or may become pregnant while receiving the drug. Leuprolide acetate injection may cause fetal harm when administered to a pregnant woman. Therefore, the possibility exists that spontaneous abortion may occur if the drug is administered during pregnancy. If this drug is administered during pregnancy or if the patient becomes pregnant while taking any formulation of leuprolide, the patient should be apprised of the potential hazard to the fetus.

WARNINGS

Initially, leuprolide acetate injection, like other LH-RH agonists, causes increases in serum levels of testosterone. Transient worsening of symptoms, or the occurrence of additional signs and symptoms of prostate cancer, may occasionally develop during the first few weeks of leuprolide acetate injection treatment. A small number of patients may experience a temporary increase in bone pain, which can be managed symptomatically. As with other LH-RH agonists, isolated cases of ureteral obstruction and spinal cord compression have been observed, which may contribute to paralysis with or without fatal complications.

Safe use of leuprolide acetate in pregnancy has not been established clinically. Before starting treatment with Leuprolide, pregnancy must be excluded (see CONTRAINDICATIONS section).

Periodic monitoring of serum testosterone and prostate specific antigen (PSA) levels is recommended, especially if the anticipated clinical or biochemical response to treatment has not been achieved. It should be noted that results of testosterone determinations are dependent on assay methodology. It is advisable to be aware of the type and precision of the assay methodology to make appropriate clinical and therapeutic decisions.

PRECAUTIONS

Patients with metastatic vertebral lesions and/or with urinary tract obstruction should be closely observed during the first few weeks of therapy (see **WARNINGS** and **ADVERSE REACTIONS** sections).

Patients with known allergies to benzyl alcohol, an ingredient of the drug's vehicle, may present symptoms of hypersensitivity, usually local, in the form of erythema and induration at the injection site.

Information For Patients

See **Information for Patients** which appears after the **REFERENCE** section.

Laboratory Tests

Response to leuprolide acetate should be monitored by measuring serum levels of testosterone and prostate-specific antigen (PSA). In the majority of patients, testosterone levels increased above baseline during the first week, declining thereafter to baseline levels or below by the end of the second week of treatment. Castrate levels were reached within two to four weeks and once attained were maintained for as long as drug administration continued.

Drug Interactions

See **CLINICAL PHARMACOLOGY — Pharmacokinetics** section.

Drug/Laboratory Test Interactions

Administration of leuprolide acetate in therapeutic doses results in suppression of the pituitary-gonadal system. Normal function is usually restored within 4 to 12 weeks after treatment is discontinued.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Two-year carcinogenicity studies were conducted in rats and mice. In rats, a dose-related increase of benign pituitary hyperplasia and benign pituitary adenomas was noted at 24 months when the drug was administered subcutaneously at high daily doses (0.6 to 4 mg/kg). There was a significant but not dose-related increase of pancreatic islet-cell adenomas in females and of testicular interstitial cell

adenomas in males (highest incidence in the low dose group). In mice no pituitary abnormalities were observed at a dose as high as 60 mg/kg for two years. Patients have been treated with leuprolide acetate for up to three years with doses as high as 10 mg/day and for two years with doses as high as 20 mg/day without demonstrable pituitary abnormalities.

Mutagenicity studies have been performed with leuprolide acetate using bacterial and mammalian systems. These studies provided no evidence of a mutagenic potential.

Clinical and pharmacologic studies in adults (≥ 18 years) with leuprolide acetate and similar analogs have shown full reversibility of fertility suppression when the drug is discontinued after continuous administration for periods of up to 24 weeks. However, no clinical studies have been conducted with leuprolide acetate to assess the reversibility of fertility suppression.

Pregnancy

Teratogenic Effects

Pregnancy Category X

(See **CONTRAINDICATIONS** and warnings sections.)

When administered on day 6 of pregnancy at test dosages of 0.00024, 0.0024, and 0.024 mg/kg (1/600 to 1/6 the human dose) to rabbits, leuprolide acetate injection produced a dose-related increase in major fetal abnormalities. Similar studies in rats failed to demonstrate an increase in major fetal malformations throughout gestation. There was increased fetal mortality and decreased fetal weights with the two higher doses of leuprolide acetate injection in rabbits and with the highest dose in rats. The effects on fetal mortality are expected consequences of the alterations in hormonal levels brought about by this drug.

Nursing Mothers

It is not known whether leuprolide acetate is excreted in human milk. Leuprolide acetate injection should not be used by nursing mothers.

Pediatric Use

See labeling for Leuprolide Acetate Injection for Pediatric Use for the safety and effectiveness in children with central precocious puberty.

Geriatric Use

In the clinical trials for leuprolide acetate injection, the majority (69%) of subjects studied were at least 65 years of age. Therefore, the labeling reflects the pharmacokinetics, efficacy and safety of leuprolide acetate injection in this population.

ADVERSE REACTIONS

Clinical Trials

In the majority of patients testosterone levels increased above baseline during the first week, declining thereafter to baseline levels or below by the end of the second week of treatment. This transient increase was occasionally associated with a temporary worsening of signs and symptoms, usually manifested by an increase in bone pain. (See **WARNINGS** section.) In a few cases a temporary worsening of existing hematuria and urinary tract obstruction occurred during the first week. Temporary weakness and paresthesia of the lower limbs have been reported in a few cases.

Potential exacerbations of signs and symptoms during the first few weeks of treatment is a concern in patients with vertebral metastases and/or urinary obstruction which, if aggravated, may lead to neurological problems or increase the obstruction.

In a comparative trial of leuprolide acetate injection versus DES, in 5% or more of the patients receiving either drug, the following adverse reactions were reported to have a possible or probable relationship to drug as ascribed by the treating physician. Often, causality is difficult to assess in patients with metastatic prostate cancer. Reactions considered not drug related are excluded.

	LEUPROLIDE ACETATE INJECTION (N=98)	DES (N=101)
	Number of Reports	
Cardiovascular System		
Congestive heart failure	1	5
ECG changes/ischemia	19	22
High blood pressure	8	5
Murmur	3	8
Peripheral edema	12	30
Phlebitis/thrombosis	2	10
Gastrointestinal System		

Anorexia	6	5
Constipation	7	9
Nausea/vomiting	5	17
Endocrine System		
*Decreased testicular size	7	11
*Gynecomastia/breast tenderness or pain	7	63
*Hot flashes	55	12
*Impotence	4	12
Hemic and Lymphatic System		
Anemia	5	5
Musculoskeletal System		
Bone pain	5	2
Myalgia	3	9
Central/Peripheral Nervous System		
Dizziness/light-headedness	5	7
General pain Headache	13	13
Insomnia/sleep disorders	7	4
	7	5
Respiratory System		
Dyspnea	2	8
Sinus congestion	5	6
Integumentary System		
Dermatitis	5	8
Urogenital System		
Frequency/urgency	6	8
Hematuria	6	4
Urinary tract infection	3	7
Miscellaneous		
Asthenia	10	10

*Physiologic effect of decreased testosterone.

In this same study, the following adverse reactions were reported in less than 5% of the patients on leuprolide acetate injection. *Cardiovascular System*-Angina, Cardiac arrhythmias, Myocardial infarction, Pulmonary emboli; *Gastrointestinal System*-Diarrhea, Dysphagia, Gastrointestinal bleeding, Gastrointestinal disturbance, Peptic ulcer, Rectal polyps; *Endocrine System*-Libido decrease, Thyroid enlargement; *Musculoskeletal System* -Joint pain; *Central/Peripheral Nervous System*-Anxiety, Blurred vision, Lethargy, Memory disorder, Mood swings, Nervousness, Numbness, Paresthesia, Peripheral neuropathy, Syncope/blackouts, Taste disorders; *Respiratory System*-Cough, Pleural rub, Pneumonia, Pulmonary fibrosis; *Integumentary System*-Carcinoma of skin/ear, Dry skin, Ecchymosis, Hair loss, Itching, Local skin reactions, Pigmentation, Skin lesions; *Urogenital System*-Bladder spasms, Dysuria, Incontinence, Testicular pain, Urinary obstruction; *Miscellaneous*-Depression, Diabetes, Fatigue, Fever/chills, Hypoglycemia, Increased BUN, Increased calcium, Increased creatinine, Infection/inflammation, Ophthalmologic disorders, Swelling (temporal bone).

In an additional clinical trial and from long-term observation of both studies, the following additional adverse events (excluding those considered not drug related) were reported for patients receiving Leuprolide.

Cardiovascular System—Bradycardia, Cardoid bruit, Extrasystole, Palpitations, Perivascular cuffing (eyes), Ruptured aortic aneurysm, Stroke, Tachycardia, Transient ischemic attack; *Gastrointestinal System*—Flatus, Dryness of mouth and throat, Hepatitis, Hepatomegaly, Occult blood (rectal exam), Rectal fistula/erythema; *Endocrine System*—Libido increase; Thyroid nodule; *Musculoskeletal System*—Ankylosing spondylosis, Arthritis, Blurred disc margins, Bone fracture, Muscle stiffness, Muscle tenderness, Pelvic fibrosis, Spasms/cramps; *Central/Peripheral Nervous System*—Auditory hallucinations/tinnitus, Decreased hearing, Decreased reflexes Euphoria, Hyperreflexia, Loss of smell, Motor deficiency; *Respiratory System*—Chest tightness, Decreased breathing sounds, Hemoptysis, Pleuritic chest pain, Pulmonary infiltrate, Rales/rhonchi, Rhinitis, Strep throat, Wheezing/bronchitis; *Integumentary System*—Boil (pubic), Bruises, Hives, Keratosis, Mole, Shingles, Spiders; *Urogenital System*—Blisters on penis, Inguinal hernia, Penile swelling, Post void residual Prostatic pain, Pyuria; *Miscellaneous*—Abdominal distention, Facial swelling/edema, Feet burning, Flu, Eyelid growth, Hypoproteinemia, Accidental injury, Knee effusion, Mass, Pallid, Sallow, Weakness.

POSTMARKETING

During postmarketing surveillance which includes other dosage forms and other patient populations, the following adverse events were reported.

Symptoms consistent with an anaphylactoid or asthmatic process have been rarely (incidence rate of about 0.002%) reported. Rash, urticaria, and photosensitivity reactions have also been reported.

Localized reactions including induration and abscess have been reported at the site of injection.

Symptoms consistent with fibromyalgia (e.g., joint and muscle pain, headaches, sleep disorders, gastrointestinal distress, and shortness of breath) have been reported individually and collectively.

Cardiovascular System - Hypotension, Myocardial infarction; *Endocrine System* - Diabetes; *Gastrointestinal System* - Hepatic dysfunction; *Hemic and Lymphatic System* - Decreased WBC; *Integumentary System* - Hair growth; *Central/Peripheral Nervous System* - Spinal fracture/paralysis, Hearing disorder; *Miscellaneous* - Hard nodule in throat, Weight gain, Increased uric acid; *Musculoskeletal System* - Tenosynovitis-like symptoms; *Respiratory System* - Respiratory disorders.

Changes in Bone Density-Decreased bone density has been reported in the medical literature in men who have had orchiectomy or who have been treated with an LH-RH agonist analog. In a clinical trial, 25 men with prostate cancer, 12 of whom had been treated previously with leuprolide acetate for at least six months, underwent bone density studies as a result of pain. The leuprolide-treated group had lower bone density scores than the nontreated control group. It can be anticipated that long periods of medical castration in men will have effects on bone density.

Pituitary apoplexy: During post-marketing surveillance, rare cases of pituitary apoplexy (a clinical syndrome secondary to infarction of the pituitary gland) have been reported after the administration of gonadotropin-releasing hormone agonists. In a majority of these cases, a pituitary adenoma was diagnosed, with a majority of pituitary apoplexy cases occurring within 2 weeks of the first dose, and some within the first hour. In these cases, pituitary apoplexy has presented as sudden headache, vomiting, visual changes, ophthalmoplegia, altered mental status, and sometimes cardiovascular collapse. Immediate medical attention has been required.

OVERDOSAGE

In rats, subcutaneous administration of 250 to 500 times the recommended human dose, expressed on a per body weight basis, resulted in dyspnea, decreased activity, and local irritation at the injection site. There is no evidence at present that there is a clinical counterpart of this phenomenon. In early clinical trials with leuprolide acetate doses as high as 20 mg/day for up to two years caused no adverse effects differing from those observed with the 1 mg/day dose.

DOSAGE AND ADMINISTRATION

The recommended dose is 1 mg (0.2 mL or 20 unit mark) administered as a single daily subcutaneous injection. As with other drugs administered chronically by subcutaneous injection, the injection site should be varied periodically. Each 0.2 mL contains 1 mg of leuprolide acetate, sodium chloride for tonicity adjustment, 1.8 mg of benzyl alcohol as preservative and water for injection. The pH may have been adjusted with sodium hydroxide and/or acetic acid. Follow pictorial directions on the reverse side of this package insert for administration.

NOTE: As with all parenteral products, inspect the solution for discoloration and particulate matter before each use.

HOW SUPPLIED

Leuprolide Acetate Injection is a sterile solution, supplied as follows:

NDC Number	Strength	Package
0703-4014-18	1 mg/0.2 mL	2.8 mL Multiple Dose Vial One multiple-dose vial per one 14-Day Patient Administration Kit

Store below 25°C (77° F). DO NOT FREEZE. Protect from light. Store vial in carton until contents are used.

REFERENCES

1. Taylor, JD. Anaphylactic reaction to LHRH analogue, leuprorelin. *Med J Australia* 1994 Oct; 161(3): 455.
2. Letterie GS, et al. Recurrent anaphylaxis to a depot form of GnRH analogue. *Obstet Gynecol* 1991 Nov; 78: 943-946.

INFORMATION FOR PATIENTS

Be sure to consult your physician with any questions you may have or for information about leuprolide acetate injection and its use.

What is leuprolide acetate injection?

Leuprolide acetate injection is chemically similar to gonadotropin releasing hormone (GnRH or LH-RH) a hormone which occurs naturally in your body.

Normally, your body releases small amounts of LH-RH and this leads to events which stimulate the production of sex hormones. However, when you inject leuprolide acetate injection, the normal events that lead to sex hormone production are interrupted and testosterone is no longer produced by the testes.

Leuprolide acetate injection must be injected because, like insulin which is injected by diabetics, leuprolide acetate injection is inactive when taken by mouth.

If you were to discontinue the drug for any reason, your body would begin making testosterone again.

DIRECTIONS FOR USING LEUPROLIDE ACETATE INJECTION

1. Wash hands thoroughly with soap and water.
2. If using a new bottle for the first time, flip off the plastic cover to expose the grey rubber stopper. Wipe metal ring and rubber stopper with an alcohol wipe each time you use leuprolide acetate injection. Check the liquid in the container. If it is not clear or has particles in it, **DO NOT USE IT**. Exchange it at your pharmacy for another container.
3. Remove outer wrapping from one syringe. Pull plunger back until the tip of the plunger is at the 0.2 mL or 20 unit mark.
4. Take cover off needle. Push the needle through the center of the rubber stopper on the leuprolide acetate injection bottle.
5. Push the plunger all the way in to inject air into the bottle.
6. Keep the needle in the bottle and turn the bottle upside down. Check to make sure the tip of the needle is in the liquid. Slowly pull back on the plunger, until the syringe fills to the 0.2 mL or 20 unit mark.
7. Toward the end of a two-week period, the amount of leuprolide acetate injection left in the bottle will be small. Take special care to hold the bottle straight and to keep the needle tip in liquid while pulling back on the plunger.
8. Keeping the needle in the bottle and the bottle upside down, check for air bubbles in the syringe. If you see any, push the plunger slowly in to push the air bubble back into the bottle. Keep the tip of the needle in the liquid and pull the plunger back again to fill to the 0.2 mL or 20 unit mark.
9. Do this again if necessary to eliminate air bubbles.
10. To protect your skin, inject each daily dose at a different body spot.
11. Choose an injection spot. Cleanse the injection spot with another alcohol wipe.
12. Hold the syringe in one hand. Hold the skin taut, or pull up a little flesh with the other hand, as you were instructed.
13. Holding the syringe as you would a pencil, thrust the needle all the way into the skin at a 90° angle. Push the plunger to administer the injection.
14. Hold an alcohol wipe down on your skin where the needle is inserted and withdraw the needle at the same angle it was inserted.
15. Use the disposable syringe only once and dispose of it properly as you were instructed. Needles thrown into a garbage bag could accidentally stick someone. **NEVER LEAVE SYRINGES, NEEDLES OR DRUGS WHERE CHILDREN CAN REACH THEM.**

SOME SPECIAL ADVICE

- You may experience hot flashes when using leuprolide acetate injection. During the first few weeks of treatment you may experience increased bone pain, increased difficulty in urinating, and less commonly but most importantly, you may experience the onset or aggravation of nerve symptoms. In any of these events, discuss the symptoms with your doctor. Like other treatment options, leuprolide acetate injection may cause impotence. Notify your doctor if you develop new or worsened symptoms after beginning leuprolide acetate injection treatment.
- You may experience some irritation at the injection site, such as burning, itching or swelling. These reactions are usually mild and go away. If they do not, tell your doctor.
- If you have experienced an allergic reaction to other drugs like leuprolide acetate injection, you should not use this drug.
- Do not stop taking your injections because you feel better. You need an injection every day to make sure leuprolide acetate injection keeps working for you.
- If you need to use an alternate to the syringe supplied with leuprolide acetate injection, insulin syringes should be utilized.
- When the drug level gets low, take special care to hold the bottle straight up and down and to keep the needle tip in liquid while pulling back on the plunger.

- Do not try to get every last drop out of the bottle. This will increase the possibility of drawing air into the syringe and getting an incomplete dose. Some extra drug has been provided so that you can withdraw the recommended number of doses.
- Tell your pharmacist when you will need leuprolide acetate injection so it will be at the pharmacy when you need it.
- Store below 77°F (25°C). Do not store near a radiator or other very warm place. Do not freeze. Protect from light — store vial in carton until use.
- Do not leave your drug or hypodermic syringes where anyone can pick them up.
- Keep this and all other medications out of reach of children.

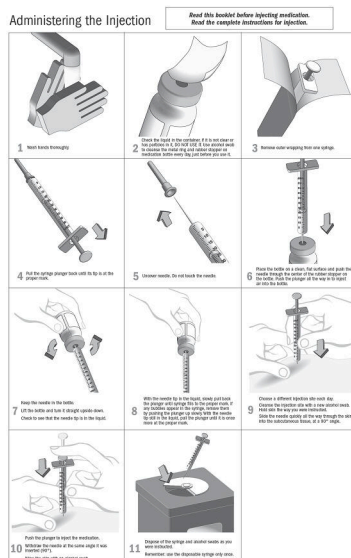
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Manufactured By:

Teva Parenteral Medicines, Inc.

Irvine, CA 92618

Administering the Injection



PRINCIPAL DISPLAY PANEL - 2.8 ML MULTIPLE DOSE VIAL LABEL

NDC 0703-4014-11 Rx only

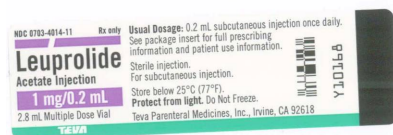
Leuprolide

Acetate Injection

1 mg/0.2 mL

2.8 mL Multiple Dose Vial

TEVA



Revised: 10/2009

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